

PTO 07-3842

German Patent No. 196 06 804 A1  
(Offenlegungsschrift)

METHOD AND CONTAINER FOR THE SCHEDULED RELEASE OF AN ACTIVE  
SUBSTANCE

Dr. Philippe Jund et al.

UNITED STATES PATENT AND TRADEMARK OFFICE  
WASHINGTON, D.C. APRIL 2007  
TRANSLATED BY THE RALPH MCELROY TRANSLATION COMPANY

FEDERAL REPUBLIC OF GERMANY  
GERMAN PATENT OFFICE  
PATENT NO. DE 196 06 804 A1  
(Offenlegungsschrift)

Int. Cl.<sup>6</sup>: A 61 K 9/50  
Filing No.: 196 06 804.5  
Filing Date: February 23, 1996  
Publication Date: August 28, 1997

METHOD AND CONTAINER FOR THE SCHEDULED RELEASE OF AN ACTIVE  
SUBSTANCE

[Verfahren und Behältnis zur planmässigen Freisetzung einer Wirksubstanz]

Inventors: Dr. Philippe Jund et al.  
Applicant: Dr. Peter Borrmann

Petition for examination has been submitted in accordance with § 44 of the patent law.

Description

The invention relates to a method for the scheduled release of an active substance, which is contained in a preferably microscopically small container, where the container releases, according to a schedule, the active substance which was previously transported in the container, particularly for medical therapy, advantageously for targeted medication.

In addition, the invention relates to a container, preferably a microcapsule, which contains an active substance and which is suitable for carrying out the mentioned method.

In medicine in particular, it is already known in principle to accommodate an active substance, for example, toxic substance, in an inert microsphere, that is, to enclose it in a preferably microscopically small container, for example, a microcapsule. For a targeted, particularly local, medication, for example, in a specifically defined organ or organ area, the container should, to the extent possible, release the active substance when it is in this target area. Thus, the container should release the active substance contained in it according to a schedule after a certain time, or after a certain path has been traveled, or at a certain place.

To date, the procedure used for this purpose has been to use a material for the container wall that decomposes after a certain time to such an extent that it then necessarily releases the active substance contained in it. The medication thus also occurred almost according to a schedule, where a calculation was made beforehand to determine at what time the container would be at a certain place, in order to adjust the temporal decomposition of the material to this time, for example, by the chosen wall thickness or the chosen material.

Nevertheless, this procedure is relatively imprecise with regard to its local target precision. In particular in the treatment of tumors or similar conditions it would be desirable for the active substance to be released from the container definitively only precisely at the place of the discovered tumor, where the time cannot be calculated and predetermined with sufficient precision.

Similar problems and purposes could also arise in the non-medical field, for example, in the transport and the target-accurate release of substances in highly sensitive, complex apparatuses.

The invention is based on the problem of allowing a targeted local release of the active substance.

The problem is solved according to the invention by the fact that the container, after a transport of the active substance, and after a predetermined local release area has been reached, is opened according to a schedule, for the targeted release of the active substance.

According to the invention, it is thus advantageous for the container to be actively opened when a local target area has been reached, so that the target-accurate release of the active substance is possible, and the uncertain method according to the state of the art is avoided, where the container is allowed to decompose over predetermined duration, and where, in the mentioned method, there is no guarantee that the predetermined local area has in fact been reached after a predetermined time. The predetermined duration can also be calculated and set only imprecisely. Moreover, the transport paths cannot always be predetermined.

In a variant of the invention, for which independent protection is also claimed, the characteristic is that an action substance which carries out the opening process by its activation, or promotes the activation, is added to the active substance into the container, where said activation is carried out in a locally targeted manner according to a plan. According to the invention, an action substance is thus added into the container, which substance is in the range [sic; position] to open the container in a quasi remote-controlled manner.

According to the invention, one possibility of opening the container consists in increasing the pressure inside the container until it bursts or ruptures open, which would be possible by increasing the entropy of the action substance and/or by increasing the kinetic energy of the action substance.

Another and optionally preferred variant of the invention, on the other hand, provides for the excitation of the action substance to perforate the container enclosure, where the container is in fact opened micromechanically.

For all the above-mentioned methods, one can consider using, according to the invention, an action substance which consists of particles that can be influenced by a magnetic field in terms of their movement and/or structure formation, where the action substance-containing container is exposed according to a schedule to a locally delimited magnetic field. For generating such a magnetic field, one can consider using a locally arranged permanent magnet, which, for example, is implanted in a human body. However, one could also consider the use of electromagnetic magnetic fields, including possibly alternating fields, generated with local delimitation, for example, with the help of computer tomograph. Using a magnetic alternating field, one could, first, increase the kinetic energy of the action substance, or, using the static field, one could increase the entropy and also trigger a mechanical action of the magnetic particles.

It is possible to use, as actuation substance, magnetic particles which form one or more annular structures, that is, which arrange themselves in the shape of a ring. When a magnetic field is applied, on the other hand, the particles align themselves in a line parallel to the field lines of the magnetic field, and thus the ring structure is broken up. It is obvious that the length of the chain structure is greater than the diameter of the ring structure was previously, so that, as a result of the formation of a thorn-like linear chain, the wall material of the container can be perforated. At the very least, the wall material can be stretched mechanically so strongly that it tears. At the same time, the linear chain structure has the higher entropy, so that additionally the interior pressure in the container increases, which also promotes the bursting of the container. As preferably-spherical magnetic particles, one can consider using particles made of magnetite or other iron oxides. Finally, any strong paramagnetic substance is suitable, which means there is a multitude of alloys that cannot be listed individually.

For a container, preferably a microcapsule, which contains an active substance, and which is suitable for carrying out the method according to the invention, an independent protection is claimed. Such a container is characterized in that it contains an action substance ~~which consists of magnetically influenceable particles.~~

~~Another variant of the invention provides for the magnetically uninfluenced particles to~~ be in a ring structure, while the magnetically influenced particles are in at least one linear chain which is oriented parallel to the magnetic field.

The container preferably has a diameter of approximately  $5 \times 10^{-7}$  m, while the diameter of a particle of the action substance is approximately  $2 \times 10^{-8}$  m.

Thus, a multitude of particles, preferably 6-14 particles, can be accommodated in the container, additionally to the active substance, so that a chain formed from these particles is reliably capable of causing the opening of the container at a predetermined place. However, an excessively long chain of particles could form a disadvantageous labyrinthine structure. The small magnetic particles themselves can be manufactured and chosen so that they are, from a medical point of view, also completely safe.

In addition, the wall of the container can be made of a material which is perforated relatively easily. For example, ~~the container according to the invention can be made of cellulose.~~ In principle, one can consider using for the wall of the container either biodegradable or nonbiodegradable substances. For example, the following would be suitable: albumin microspheres, poly(alkylcyanoacrylate) microspheres, ethylcellulose and polyglutaraldehyde microcapsules. To the extent possible, the dimensions of the container are such that it can be injected without problem, for example, into the blood circulation and transported through the finest capillary vessels to a certain local place. In the method according to the invention the time when the container reaches the target place is not essential, because it will be opened in any case only once it reaches the influence area of the locally specifically delimited generated magnetic field.

Substances that are toxic can therefore also be used for a targeted local therapy, for example, for the destruction of carcinomas, tumors or metastases, without detrimental effect on the healthy area around the organ.

An embodiment example which produces additional characteristics according to the invention is represented schematically in the drawing.

Figure 1 shows a cross section through a container according to the invention, and Figure 2 shows the container according to Figure 1 after the active opening.

Figure 1 is a schematic cross section of a container which contains an active substance, for example, a liquid, which is not represented in greater detail. In addition, the container 1, itself in the shape of a sphere, contains a number of magnetically influenceable particles 2, shown essentially with a spherical shape, which are not influenced by an external magnetic field, and have therefore combined to form a ring structure.

If an external magnetic field is applied, then the ring structure breaks up, and the magnetically influenceable particles 2 form a linear chain, as represented in Figure 2. Because of the resulting longitudinal extension of the particle chain, the container 1 is first deformed with lengthwise stretching, and finally opened, or it tears due to the pressure which is generated as a result. In addition, the entropy of the linear chain is higher compared to the ring structure, so that, inside the container, due to the increase in entropy, a higher pressure is generated which

also promotes the bursting of the container. The active substance, for example, a liquid, is released from the opened container 1.

The linear chain is aligned parallel to the field lines of the influencing magnetic field. Under some circumstances, several parallel chains can also form. However, because a relatively large number of magnetically influenceable particles must be accommodated in addition to the active substance in the container, such partial chain strands can also reach such an extent that the container is caused to tear.

The size ratios between the magnetically influenceable particles 2 and the container 1 are not represented to scale in the drawing. In actuality, the container 1 can present a diameter approximately five times greater than that of a magnetically influenceable particle 2, so that the number of such particles 2 that can be arranged in the container is very much larger than shown in the drawing.

### Claims

1. Method for the scheduled release of an active substance, which is contained in a preferably microscopically small container, where the container releases, according to a schedule, the active substance which was previously transported in the container, particularly for medical therapy, advantageously for targeted medication, characterized in that the container, after a transport of the active substance, is opened after a predetermined scheduled local release area has been reached for the targeted release of the active substance.

2. Method, preferably according to Claim 1, characterized in that an action substance, which as a result of its activation carries out or promotes the opening process, is added to the active substance into the container, where said activation is carried out in a locally targeted manner according to a schedule.

3. Method according to Claim 2, characterized in that the pressure in the interior of the container is increased until it bursts.

4. Method according to Claim 3, characterized in that the entropy, particularly the vibration entropy, of the action substance is increased.

5. Method according to Claims 3 and 4, characterized in that the kinetic energy of the action substance is increased.

6. Method according to Claim 2, characterized in that the action substance is triggered by the perforation of the container enclosure or the container wall.

7. Method according to one or more of Claims 2-6, characterized in that the action substance consists of particles movements and/or structure formation of which can be influenced by a magnetic field, and in that the action substance-containing container is exposed according to a schedule to a locally limited magnetic field.

8. Method according to Claim 7, characterized in that a locally arranged permanent magnet is used for the generation of the magnetic field.

9. Method according to Claim 7, characterized in that, an electromagnetic field, preferably a computer tomography, is used as electrical field.

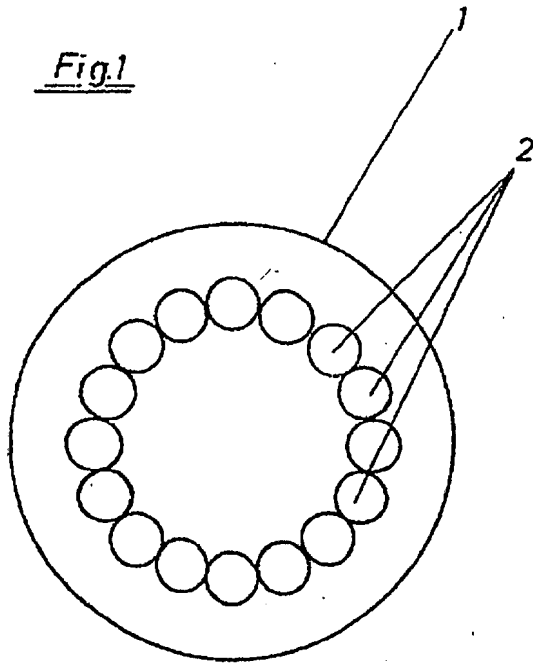
10. Method according to Claim 7, characterized in that an electromagnetic alternating field is used as magnetic field.

11. Container, preferably a microcapsule, which contains an active substance, characterized in that it contains an action substance which consists of particles that can be influenced magnetically.

12. Container according to Claim 11, characterized in that the magnetically uninfluenced particles (2) are in a ring structure, while the magnetically influenced particles (2) are in at least one linear chain which is aligned parallel to the magnetic field.

13. Container according to Claim 11 or 12, characterized in that the container (1) has a diameter of approximately  $5 \times 10^{-7}$  m, while the diameter of particle (2) of the action substance is approximately  $2 \times 10^{-8}$  m.

14. Container according to one of Claims 11-13, characterized in that the container (1) is made of cellulose.

Fig.1Fig.2